

SEMINAR

Department of Biological Sciences



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Conformational Dynamics and Allostery in Molecular Signaling

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Signaling proteins are critical communicators of the cell that are capable of sensing and responding to diverse stimuli, in the form of chemical, physical or mechanical perturbations. A major question in signaling has surrounded the mechanism for allosteric communication or how signals are propagated through proteins. These have been assumed to be linear relays analogous to molecular cables, connecting the sensor site and distal allosteric effector sites. Our group's research program has defined an alternate dynamics-based model wherein the inherent ability of proteins to exist in ensembles of multiple conformations not unlike "molecular springs" in solution, is a prerequisite for their ability to function in signaling. I will be presenting specific examples of the effects of varied perturbations on proteins that drive different steps of signaling processes: i) Sensing: Receptor responses to mechanosensory cues (Osmosensing); ii) Propagation: Posttranslational modifications of proteins via phosphorylation (Two-component signaling); iii) Activation and Desensitization: by protein-protein and ligand interactions (Second messenger cAMP signaling). Structural mass spectrometry (amide hydrogen/deuterium exchange mass spectrometry and ion mobility mass spectrometry) is a new entrant to studying protein dynamics in the millise-c-min timescales. Our research is pioneering applications of structural mass spectrometry in combination with complementary biophysical tools such as computational docking, fluorescence, mutagenesis, peptide array and X-ray crystallography to understanding allosteric regulation in signaling proteins. Lastly, I will present spin-off applications to Fragment-based drug discovery.